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Short-Term Outcomes in Newly Diagnosed Atrial Fibrillation and Chronic Kidney Disease: How Important Is Ethnicity?

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Atrial fibrillation (AF) often co-exists with other comorbidities and has an increased prevalence and incidence with worsening renal function.[1–3] Overall management of the condition includes detailed risk assessment, cardiovascular risk reduction, and stroke prevention. The latter requires appropriate use of oral anticoagulation (OAC) whether as vitamin K antagonists (eg, warfarin) or non–vitamin K antagonist oral anticoagulants (NOACs), and regional differences are evident in their uptake.[4] Nevertheless, optimal OAC use poses challenges if chronic kidney disease (CKD) is also present, given the difficulties of maintaining good anticoagulation control with warfarin[5] (leading to prognostic implications[6]) and since all NOACs have a degree of renal dependency for their excretion.[7]

The risk of stroke in AF is not homogeneous (being dependent on various stroke risk factors that have been used to formulate risk stratification schemes[8]), and presence of CKD increases stroke risk, although not additive to stroke risk stratification using the CH_2ADS_2-VASc score[9] given that many of the pre-existing components of this score are already strongly associated with renal function.

In the current issue of the *Journal of the American Heart Association* (*JAHA*), Goto et al[10] report on the impact of CKD on 1-year outcomes in patients with newly diagnosed AF. Data on 33 024 patients from the international, prospective GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) were analyzed. They found that mild and moderate-to-severe CKD were independently associated with increased adjusted all-cause mortality at 1-year, adjusted hazard ratio of 1.45 (95% CI 1.26–1.66) and 1.82 (95% CI 1.59–2.09), respectively. After adjusting for baseline characteristics and antithrombotic use, moderate-to-severe CKD was independently associated with increased 1-year risk of stroke/systemic embolism, major bleeding, all-cause mortality, cardiovascular/noncardiovascular mortality, new-onset acute coronary syndrome, and heart failure.

Perhaps the most interesting finding in the study is the different impact of CKD among patients from Asia compared with the rest of the world (RoW) (Figure). Patients from Asia with newly diagnosed AF and no CKD have a lower 1-year all-cause mortality of 2.2% (95% CI 2.05–2.77) compared with the RoW of 3.4% (95% CI 3.31–3.91). At first glance, it would appear that mild CKD does not contribute to any increase in all-cause mortality among patients from Asia as it does for the RoW. However, moderate-to-severe CKD causes a dramatic rise in all-cause mortality among patients from Asia such that their increased mortality (adjusted hazard ratio of 2.44, 95% CI 1.83–3.26) significantly exceeds that for RoW (adjusted hazard ratio of 1.64, 95% CI 1.41–1.90).

Before attempting to rationalize this, a few points deserve stating. First, patients from Asia had a lower body mass index, prevalence of coronary artery disease, hypertension, and hypercholesterolemia. While hazard ratios were adjusted for various factors including hypertension, none of the other formerly mentioned factors were taken into account. Secondly, as acknowledged by the authors, the severity of CKD was classified by individual investigators and no laboratory data on renal function were collected. This has a potential for major bias. More importantly, the methods used to determine estimated glomerular filtration rate were not standardized. It has previously been shown that the discriminant capability for the 1-year risk of death in AF differed with various estimated glomerular filtration calculation algorithms (Table): The best was the Cockroft-Gault equation adjusted for body surface area, followed by Cockroft-Gault, Chronic Kidney Disease Epidemiology Collaboration, and Modification of Diet in Renal Disease equations.[11–14] Additionally, several studies have demonstrated ethnic variations in normal reference

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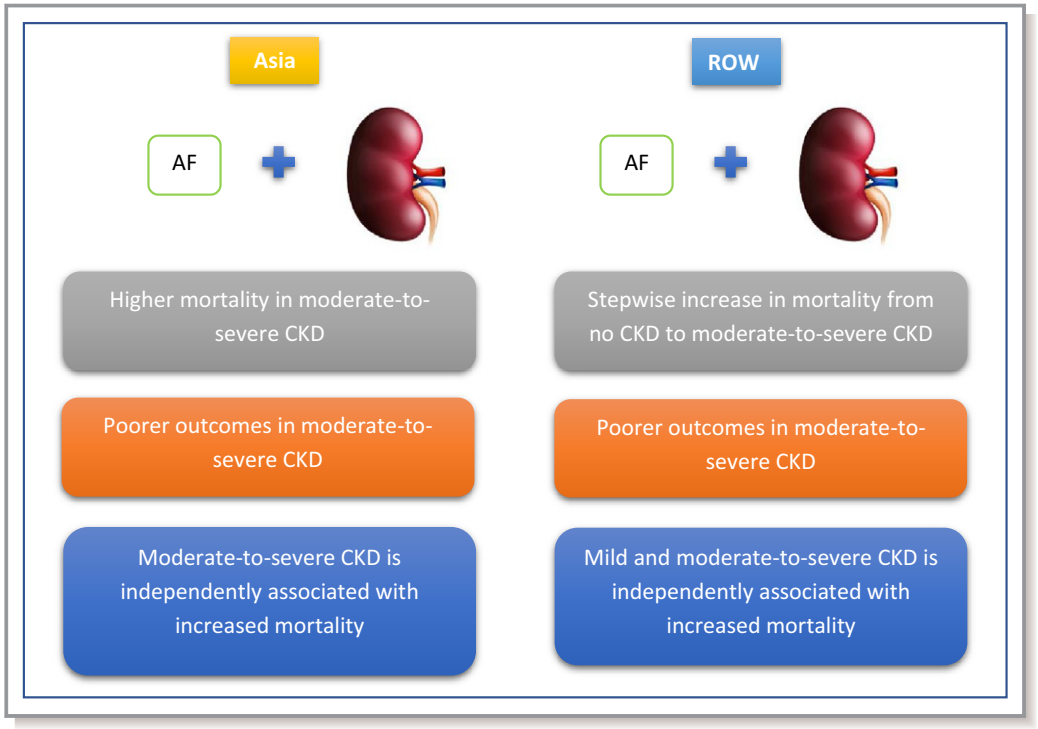

Figure. The role of chronic kidney disease in patients with atrial fibrillation from Asia vs rest of the world (ROW)—results from GARFIELD-AF registry. AF indicates atrial fibrillation; CKD, chronic kidney disease.

values for glomerular filtration rate,[15–17] which may be improved with the inclusion of an ethnic coefficient.[11]

A previous study reported lower mortality rates in Asian patients with CKD compared with whites.[18] Therefore, in context of the results reported by Goto et al,[10] it may be postulated that the presence of newly diagnosed AF in an Asian population with advanced CKD alters the risk profile significantly such that these patients experience a dramatic rise in 1-year all-cause mortality, and any protective effects that are conferred by ethnicity, environmental factors, or lifestyle are lost. Alternatively, this may reflect ineffective overall management of patients with moderate-to-severe CKD in Asia.[18]

The study found that in Asia compared with the RoW, there was less frequent use of vitamin K antagonist±antiplatelet therapy, but increased use of both antiplatelet monotherapy

Table. Formulae to Calculate Estimated Glomerular Filtration Rate

Name	Equation			
Cockroft-Gault[12]	(140−age)×(weight, kg)×(0.85 if female)/(72×Cr) IBW, kg (male)=50+[2.3×(height, inches−60)] IBW, kg (female)=45.5+[2.3×(height, inches−60)]			
Chronic Kidney Disease Epidemiology Collaboration[13]	A×(SCr/B)C×0.993 age×(1.159 if black), where A, B, and C are the following:			
	Female		Male	
	SCr ≤0.7	A=144	SCr ≤0.9	A=141
		B=0.7		B=0.9
		C=−0.329		C=−0.411
	SCr ≥0.7	A=144	SCr ≥0.9	A=141
		B=0.7		B=0.9
		C=−1.209		C=−1.209
Modification of Diet in Renal Disease[14]	186×Serum Cr−1.154×age−0.203×1.212 (if patient is black)×0.742 (if female)			

Cr indicates creatinine; IBW, ideal body weight; SCr, serum creatinine.

and no antithrombotic therapy, as well as comparable rates of NOACs±antiplatelets. In addition, patients in Asia treated with vitamin K antagonists were less likely to achieve time in therapeutic range≥65% for target international normalized ratio of 2.0 to 3.0 (no/mild CKD: 19.8% in Asia versus 46.3% in RoW and moderate-to-severe CKD: 16.0% in Asia versus 44.4% in RoW).

These data on poorer time in therapeutic range are supportive of the increased efficacy and safety with NOACs in Asians compared with non-Asians.[19,20] Despite the disparity in antithrombotic management, observed stroke/systemic embolism and major bleeding rates were rather similar for both regions and CKD groups. However, event rates were low and hence true differences may not have been detected.

Several limitations are inherent when performing studies such as this using registry data. An important limitation to consider is that the CKD stage was assessed only at the time of enrollment and therefore did not account for possible time-dependent changes in renal function. Asian patients have previously been reported to have faster progression of CKD.[18] While taking into account time-dependent change in renal function is less important when assessing short-term outcomes, it is imperative that future studies with longer follow-up include this to enable accurate assessment of the effects of renal function on morbidity and mortality outcomes in patients with AF.

In summary, the study by Goto et al[10] has demonstrated a negative impact of CKD in newly diagnosed AF patients, with greater effect seen in moderate-to-severe CKD patients from Asia. Future studies are needed to confirm the findings and evaluate the ethnic differences reported here.

Disclosures

Lip reports consulting for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Gupta reports speaking for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Biosense Webster, and Boston Scientific. Proctor for Abbott and Research Grants from Medtronic, Biosense Webster, and Boston Scientific. The remaining authors have no disclosures to report.

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